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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 54

Application Number: 08/453,350
Filing Date: 5/30/95
Appellant(s): HELDIN et al.

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For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 26 January 2001.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because it does not indicate that it is directed to a PDGF A-chain homodimer "such that the protein preparation is free of other human proteins" as alleged in the Summary of the Invention. The specification fails to recite this language. The specification indicates that the invention is directed to "[r]ecombinant PDGF comprised of PDGF A-chain polypeptide" (see page 3, lines 21-22).

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 25-27, 43-45 and 55-66 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Heldin et al. "A human osteosarcoma cell line secretes a growth factor structurally related to a homodimer of PDGF A-chains." Nature, vol. 319 (1986), pp. 511-514.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 25-27, 43-45, and 55-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Heldin et al. (Nature 319: 511-514, 1986).

Heldin teaches a PDGF AA homodimer (ODGF) derived from osteosarcoma cells which is disulfide linked (p. 511, col. 2). Although the entire amino acid sequence of the PDGF AA homodimer was not determined, N-terminal sequencing of the homodimer yielded a sequence which was identical to the N-terminal sequence of the A chain of PDGF (p. 512). Although the exact number of amino acids in each A chain was not determined, as recited in the instant claims, Heldin discloses that the purified PDGF AA had agonist activity and was recognized by antibodies against PDGF (p. 511), such that the PDGF AA taught by Heldin is deemed to meet the limitations of the claims, absent evidence to the contrary. Furthermore, although Heldin does not disclose a recombinant PDGF AA homodimer, as recited, a product by process limitation for a composition is considered only insofar as it alters the composition. In the absence of evidence to the contrary, the recombinant protein of the claims is considered identical to the prior art protein purified from nature, as disclosed by Heldin.

The instant claims recite "free of other human proteins", however, the protein isolated by Heldin et al. Appears to be highly pure and free of other human proteins, since there are no bands other than PDGF AA in the protein preparation which are visible after SDS PAGE and silver staining of the gel (see Fig. 1, p. 512). It is well-known in the art that silver staining is

one of the most highly sensitive methods of determining whether there are any protein contaminants in a preparation. In addition, Heldin state that no other amino acid sequence was obtained from the purified PDGF AA preparation (p. 512). Amino acid sequence analysis is also a highly sensitive method of determining whether a protein sample is homogeneous, and Heldin et al. indicate that the preparation was homogeneous. Further, the preparation of Heldin et al. also appears to be free of virus contamination because the protein was derived from conditioned medium of cells growth in a laboratory (Fig. 1 legend, p. 512), which would be highly unlikely to be contaminated with virus.

2. Claims 55-57 are rejected under 35 U.S.C. 103(a) as obvious over Heldin et al.

The disclosure of Heldin is provided above. Heldin et al. is not clear at to whether the purified composition was in a pharmaceutically acceptable carrier prior to the final gel analysis, which confirmed the purity of the composition. However, it would have been *prima facie* obvious to one of ordinary skill in the art to dialyze the composition which was eluted from the HPLC column in 0.01M phosphate buffer at pH 7.4 as was previously done in the method in order to obtain a composition in a pharmaceutically acceptable carrier in order to test the biological activity of the composition on human foreskin fibroblasts. One would necessarily need to place the composition in such a carrier in order to administer it to fibroblasts because the high acetic acid concentration from the HPLC column would adversely

affect the fibroblasts. Therefore, the invention as a whole would have been *prima facie* obvious, absent evidence to the contrary.

(11) Response to Argument

At page 10 of the Brief, Appellant asserts that "[t]he Examiner has failed to consider this evidence and has instead improperly substituted her own personal knowledge without providing an affidavit establishing her credentials as a person of ordinary skill or presenting the facts relied upon to the exclusion of those presented in the evidence submitted by Appellants". This assertion is unfounded in that all evidence and arguments have been carefully considered, and upon consideration of all evidence and arguments, the Examiner arrived at a conclusion that differed from that of Appellants. This does not equate to "substituting her own personal knowledge" and no such "personal knowledge" has been referenced in the grounds of rejection.

At page 10 of the Brief, Appellant urges that Heldin does not disclose (1) a specific amino acid sequence for PDGF A homodimer, (2) a recombinantly produced protein from a non-human cell, and (3) a protein that is free of other human proteins. These arguments are not persuasive. First, the protein of Heldin has been identified as PDGF A , which is a homodimer, therefore, it would inherently possess the amino acid sequence of the instant claims. Appellant as offered no evidence to contradict this conclusion. Such evidence would may obviate the instant ground of rejection since the claims rely on a specific amino acid

sequence. Second, Appellant argues that Heldin fails to disclose a protein preparation produced recombinantly from nonhuman cells. However, the limitation of recombinantly produced from nonhuman cells is a product by process limitation. Patentability depends on whether the product is known in the art or obvious, and is not governed by its process of production (In re Klug, 142 USPQ 161); therefore, the burden is upon applicants to establish a patentable difference (In re Fessman, 180 USPQ 324). Further held was that when a prior art product reasonably appears to be the same as the claimed, but differs by process in which it was produced, a rejection of this nature is eminently fair and the burden is upon appellants to prove, by comparative evidence, a patentable difference (In re Brown, 173 USPQ 685; In re Marosi, 218 USPQ 289; In re Thorpe, 227 USPQ 965; In re Fitzgerald, 205 USPQ 594; and as more recently emphasized in Ex parte Gray, 10 USPQ2d 1922; Amgen Inc. v. Chugai Pharmaceutical Co., 9 USPQ2d 1822; and Scripps Clinic v. Genentech Inc., 3 USPQ2d 1481). Furthermore, in a recent court decision regarding proteins, the decisional law held that recombinantly produced proteins are not patentable or functionally distinct from their native counterpart proteins (Ex parte Gray, 10 USPQ2d 1922; Amgen Inc. v. Chugai, 9 USPQ2d 1833; and Scripps v. Genentech, 3 USPQ2d 1481). In view of the fact that the courts have clearly emphasized that product claims unless there has been established a patentable difference, one having ordinary skill in the art at the time of the invention would have expected that the PDGF produced by the recombinant process of the instant claims would be functionally/biologically equivalent to native PDGF as produced by Heldin and would

therefore function in a manner taught by the prior art. Thirdly, Appellant argues that Heldin's protein preparation is not free of other human proteins. Appellant has not offered any comparative evidence to support this conclusion. As stated in the grounds of rejection, the protein of Heldin was homogeneous as evidenced by a single band on a silver stained gel and the absence of any other amino acid sequence present in the preparation. The claims fail to recite free of "all other human proteins", therefore, the claims fail to exclude any potential trace proteins. Further, there is no comparative evidence of record to demonstrate that there were any other proteins present in the Heldin preparation.

Appellant argues at page 11 of the Brief that "Heldin did not disclose to persons of ordinary skill in the art at the time of invention a protein preparation comprised of a PDGF A-chain homodimer" because the reference did not explicitly state that the ODGF protein was PDGF A homodimer. This argument is not persuasive because all properties of a compound, whether disclosed in the prior art or not, are inherently possessed by the compound of the prior art. In re Papesch, 315 F.2d 381, 137 USPQ 42, 51 (CCPA 1963) held that "From the standpoint of patent law, a compound and all its properties are inseparable." The Declaration of Betsholtz implicitly states that the ODGF of the Heldin reference is now known "to be the same as a naturally occurring PDGF A-chain homodimer". Therefore, the prior art of Heldin clearly discloses a protein preparation comprised of a PDGF A-chain homodimer.

Appellant argues at pages 11-12 that the prior art fails to teach a recombinantly produced protein in a non-human cell. Appellant is correct in this regard. However, the

recitation of recombinantly produced fails to distinguish the claimed protein from the protein of the prior art for the reasons of record. As stated previously, the courts have held that when a prior art product reasonably appears to be the same as the claimed, but differs by process in which it was produced, a rejection of this nature is eminently fair and the burden is upon Appellants to prove, by comparative evidence, a patentable difference. No such comparative evidence has been submitted. Appellant urges that the recombinantly produced protein is free of other human proteins, and that the protein of Heldin "necessarily contains other proteins". This argument is not persuasive because the evidence of record suggests that the protein of Heldin is a homogeneous preparation in which no other proteins were detected. Further, it is submitted that it is "free of other human proteins" because the recitation of "free of other human proteins" does not equate to "free of all human proteins". Appellant refers to free of pathogenic viruses, however, it should be noted that this is not a limitation of the instant claims.

Appellant asserts that Heldin "fails to disclose a protein preparation that is free of other human proteins and/or pathogenic viruses" (see page 13 of the Brief). This argument is not persuasive because the single protein band on the silver stained gel of Heldin clearly demonstrates that the protein preparation was "free of other human proteins", as well as the statement that the preparation was homogeneous. Appellant refers to free of pathogenic viruses, however, it should be noted that this is not a limitation of the instant claims.

Appellant argues that a single silver stained band on a gel would not be understood by one of skill in the art as conclusive evidence of homogeneity (see page 13 of the Brief). This argument is not persuasive because Heldin states that the preparation was homogeneous, and Appellant has failed to offer any comparative evidence to rebut this showing or conclusion. The Cousens Declaration has been carefully considered, however, the statements contained therein are not specific to the protein preparation at hand, and in the absence of comparative evidence, it would appear that the preparation of the prior art is homogeneous, and is clearly "free of other human proteins".

Appellant also argues that the presence of a single amino acid sequence in the protein preparation is not evidence of a homogeneous composition because some proteins will be "blocked". However, it would appear unlikely that every other possible contaminating protein would be "blocked", wherein, only a single amino acid sequence would be obtained when there were contaminants in the preparation. Appellant's arguments are hypothetical suggestions which have not been demonstrated to have occurred in the preparation of Heldin et al. While it is appreciated that there are limitations with both methods in making a determination of protein homogeneity, the use of both techniques, wherein both demonstrate a homogeneous preparation, is suggestive that the preparation of Heldin is homogenous and is clearly "free of other human proteins", absent evidence to the contrary. The Cousens declaration does not provide comparative evidence. Further, the claims do not require that the preparation be free of all human proteins, but only "free of other human proteins", and it

would appear from the evidence of record that the homogeneous preparation of Heldin is "free of other human proteins".

Appellant argues at page 14 of the Brief that the Kornberg reference establishes that isolation of a protein according to the methods of Heldin cannot result in a protein preparation that is free of other human proteins. This argument is not persuasive for a number of reasons. First, the instant specification does not define "free of other human proteins". Since the claims do not recite free of all other human proteins, it is asserted that this recitation does not encompass absolute purity. Since the claims do not encompass absolute purity, the preparation of Heldin meets the limitations of the claims. If the claims intend absolute purity, it is asserted that the instant claims are not enabled, because the preparation of a protein from a recombinant cell requires manipulation by a technician, which would ultimately result in contamination, which would not equate to absolute purity. Secondly, the reference of Kornberg does not address the specifics of the instant rejection. As stated previously, a *prima facie* case has been made that the preparation of Heldin anticipates the instant claims, and Appellant has not come forward with comparative data to dispute the *prima facie* case. Appellant continues by stating that the declarations of Cousens and Betsholtz contend that purification of proteins from human sources cannot result in a preparation which is free of contaminating human proteins. However, as stated previously, the recombinantly produced protein will also result in contamination by human proteins, therefore, it is not clear what

degree "free of other human proteins" is meant to encompass, and it would appear that the preparation of the prior art meets the limitations of the instant claims.

Appellant urges at pages 15-16 of the Brief that the "Examiner is in error" and that the Office "has failed to adequately consider and rebut the facts and reasoned conclusions presented in the Cousens and Betsholtz Declarations regarding key elements of the claimed invention". This argument is not persuasive for the reasons presented above. As to the adequacy of the consideration and rebuttal, it is for the Board to decide if the Examiner has met her burden under Marzocchi (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)).

Appellant asserts that the Declarations of Cousens and Betsholtz "completely rebut the Examiner's conclusion". However, the Examiner did not arrive at that conclusion because the declarations fail to address the meaning of the recitation "free of other human proteins" and fail to provide comparative evidence to rebut the findings of Heldin. Appellant's arguments spanning pages 17-19 have been previously presented and answered in the instant response.

Appellant again asserts that "the Examiner has improperly and repeatedly dismissed the Declatory evidence of record with conclusory statements to the effect that there is no evidence or record which supports a conclusion that there were any other proteins present in the preparation of Heldin" and is "substituting her own personal knowledge for that of Dr. Cousens and Dr. Betsholtz". This assertion is not persuasive because the Examiner has carefully considered all of the evidence, declarations, and arguments and has arrived at a

conclusion that differs from Appellant. The Examiner has not relied on any personal knowledge in making the instant grounds of rejection, therefore, an affidavit is not necessary.

Appellant asserts at page 20 of the Brief that an improper standard has been applied for overcoming the 102(b) rejection. This argument is not persuasive because the court has held that when a prior art product reasonably appears to be the same as the claimed, but differs by process in which it was produced, a rejection of this nature is eminently fair and the burden is upon appellants to prove, by comparative evidence, a patentable difference (In re Brown, 173 USPQ 685; In re Marosi, 218 USPQ 289; In re Thorpe, 227 USPQ 965; In re Fitzgerald, 205 USPQ 594; and as more recently emphasized in Ex parte Gray, 10 USPQ2d 1922; Amgen Inc. v. Chugai Pharmaceutical Co., 9 USPQ2d 1822; and Scripps Clinic v. Genentech Inc., 3 USPQ2d 1481). Furthermore, in a recent court decision regarding proteins, the decisional law held that recombinantly produced proteins are not patentable or functionally distinct from their native counterpart proteins (Ex parte Gray, 10 USPQ2d 1922; Amgen Inc. v. Chugai, 9 USPQ2d 1833; and Scripps v. Genentech, 3 USPQ2d 1481). The Examiner has provided evidence and reasoning as to why the protein preparations appear to be the same, therefore, the burden of establishing a difference shifts to Appellant, and it is the court who indicated comparative evidence, not the Examiner.

Appellant argues at page 21 that hindsight reasoning was used in rejecting claims 55-57. In response to Appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on

obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Appellant argues that there is no motivation to arrive at the claimed invention. This argument is not persuasive in that motivation is provided in the grounds of rejection. Appellant's arguments presented at pages 22-23 are repetitious of those presented throughout the Brief and answered above.

Appellant's statements regarding claims 43-45 and the presence of a pharmaceutically acceptable excipient are not persuasive because it would appear that the purified composition of Heldin was in a pharmaceutically acceptable carrier prior to the final gel analysis, absent evidence to the contrary (this limitation was addressed previously in prosecution). Appellant's statements regarding claims 55-57 were addressed in the grounds of rejection. Appellant's statements regarding claims 58-63 are not persuasive because the claims encompass the naturally occurring amino acid sequence of the protein of Heldin, and do not require any modification of the naturally occurring amino acid sequence in that the analogs have "less than 10" or "3 amino acid substitutions" which encompasses no substitutions.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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